REMARKS

I. Status of the Claims

Claims 1, 3-6 and 8-13 are pending in the application. In response to the restriction requirement which the examiner imposed, applicants elected Group II, claims 3-5 and 10. Thus, claims 1, 6, 8, 9 and 11-13 stand withdrawn. Claims 3-5 and 10 stand rejected, variously, under 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants note and appreciate the examiner's entry of the previously submitted rejections as stated in the Advisory Action.

II. Rejection Under 35 U.S.C. §102

Claims 4 and 10 remain rejected as anticipated by Blankenberg *et al.*, arguing that despite applicants efforts to distance themselves from the reference on the basis of its use of Annexin V merely as a targeting component in a larger composition, the claims fail to distinguish said subject matter. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended to recite that the Annexin V of the present claims is the active component of the pharmaceutical composition. Support to be found in the application as filed at page 4 lines 15-18. The significance of this amendment is discussed in detail below.

Referring again to the Abstract of Blankenberg *et al.*:

> The present invention relies on the affinity of stressed or apoptotic cells for exogenously administered annexin V to create a multi-functional molecular probe that can be simultaneously used for imaging (localization of unstable plaque within the body) and therapy (treatment of unstable plaque).

The abstract specifically refers to the use of a "multi-functional molecular probe" that is created using annexin V, ***but not Annexin V itself***, for treatment of unstable plaques. As further presented in the previous response, the meaning of this term is clear from paragraph [0032] of Blankenberg *et al.*:

> [0032] In particular, compositions according to the present invention for detecting and treating vulnerable plaque comprise a binding molecule, a targeting molecule, and an effector molecule. The binding molecule will specifically bind to marker(s) on stressed or apoptotic cells which are characteristic of vulnerable plaque. The targeting molecule will permit localization of the composition when the composition is intravascularly bound to vulnerable plaque. Finally, the effector molecule will selectively kill or inhibit the stressed or apoptotic cells associated with vulnerable plaque. In a first specific embodiment, the binding molecule comprises annexin. In a second specific embodiment, the targeting molecule comprises a radiolabel such as technetium-99m. In a third specific embodiment, the effector molecule comprises a photodynamic agent such as a porphyrin".

Thus, the reader of Blankenberg *et al.* understands that the reference, in the Abstract, to a "multi-functional molecular probe" is reference to a multi-component complex that comprises: (a) a binding molecule, such as an annexin protein, to allow for specific binding of the "multi-functional molecular probe" to the apoptotic cells of vulnerable plaques; (b) a targeting molecule, such as technetium-99m, to allow localization of the "multi-functional molecular probe" after its administration; and (c) an ***effector*** molecule, such a photodynamic agent like porphyrin, to allow the "multi-functional molecular probe" to be activated in order to kill or inhibit the stressed or apoptotic cells following activation. From this definition, it is quite clear that the only "active component" in the complex of Blankenberg *et al.* distinct from annexin, which is purely a binding molecule, and is not even characterized by the reference is sufficient to achieve "targeting," something required by yet another component of the complex. And indeed,

there is no teaching or suggestion in the abstract or elsewhere in Blankenberg *et al.* that Annexin V itself could be useful for preventing atherosclerotic plaque rupture.

This reading of the document is entirely consistent with paragraph [0028] which teaches that "The present invention relies on the affinity of stressed or apoptotic cells for exogenously administered annexin V to create a multi-functional molecular probe ...." Also, paragraph [0029] states that "In a first embodiment, annexin V is labeled with both a radioisotope such as technetium-99m and a photodynamic agent such as a light absorbing porphyrin." Likewise, paragraph [0030] teaches that "Conversely, annexin V could be conjugated with antisense-DNA or RNA oligonucleotides with a label bond that would lyse upon entry into the target cell trapping the oligonucleotide(s) of interest within." In all these cases it is clear that Annexin V is only envisaged to be useful as a binding molecule and is not taught to have any capability itself to preventing atherosclerotic plaque rupture.

Applicants further provided an extensive rebuttal of the examiners attempted reliance on the teachings of paragraphs [0034] and [0031] of Blankenberg *et al.* In the Advisory Action, the examiner failed to comment on this line of argument, relying exclusively on the argument that the claims encompassed the multi-functional molecular probe as disclosed by Blankenberg *et al.* Given the restriction of the claims with the current amendment, applicants believe that this argument has been overcome, and incorporate their previous arguments on paragraphs [0034] and [0031] to the extent that the examiner might now attempt to argue that Annexin V alone would be considered a therapeutic candidate for preventing atherosclerotic plaque rupture based on the teachings of Blankenberg. As set out previously, such an argument would not be supported by the evidence of record.

To summarize, paragraph [0032] of Blankenberg *et al.* teaches that, in order to treat vulnerable plaques, one should ***selectively kill*** cells therein, using the disclosed multi-functional complex. Also, paragraph [0031] of Blankenberg *et al.* teaches that unlabelled Annexin V may be useful for exerting ***anti-apoptotic effects***. Apoptosis is a form of cell death, and so an anti-apoptotic effect is an effect that *prevents* cell death. The selective killing or inactivation of cells in an atherosclerotic plaque is ***the opposite*** of preserving such cells by preventing apoptosis. Accordingly, the disclosure in paragraph [0031] of Blankenberg *et al.*, which refers to using "the intrinsic anti-apoptotic effects" of Annexin V for an unspecified "therapeutic effect" clearly cannot be taken to be a teaching that one should use Annexin V itself to prevent the rupture of atherosclerotic plaques. On the contrary, from the disclosure in paragraph [0032], the skilled person would understand that ***the opposite effect***, *i.e.*, cell killing, is required to treat vulnerable plaques. Thus, paragraph [0031] of Blankenberg *et al.* is not a disclosure or suggestion that Annexin V itself should, or even could, be used to prevent the atherosclerotic plaque rupture.

Of course, in contrast to all of the preceding disclosures, the present application clearly indicates that Annexin V can, by itself, effect protection from plaque rupture. For all of the foregoing reasons, applicants submit that claims 4 and 10 are not anticipated by Blankenberg *et al.*, nor could they be rendered obvious. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

III. Rejection Under 35 U.S.C. §103

Claims 3 and 5 remain rejected as rendered obvious by Blankenberg *et al.* in view of Manzi *et al.* Once again, applicants traverse.

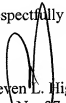
The examiner alleges that Manzi teaches that SLE patients are known to have a greater risk of plaque rupture. However, the examiner admits that Manzi *et al.* is not used to supplement any deficiencies in the teachings of Blankenberg. Thus, the examiner tacitly acknowledges that Manzi says nothing about a potential role for Annexin V in modulating plaque rupture; nor does it suggest that apoptosis should be prevented in order to prevent plaque rupture.

Thus, in light of the clear deficiencies with respect to Blankenberg *et al.* in view of the claims as submitted herewith, and the inability of Manzi *et al.* to overcome the shortcomings of Blankenberg *et al.*, as outline above, obviousness has not been established by the evidence of record. Reconsideration and withdrawal of this rejection also is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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Date: July 26, 2010